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Documents Management Branch (HFA-305)
Food and Drug Administration
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Re: Draft Guidances for Industry on Food-Contact Substance Notification System [Docket No. 99D-4575 and 99D-4576]

The Society of the Plastics Industry, Inc. (SPI)[1/] by its attorneys and through its Food, Drug and Cosmetic Packaging Materials Committee (FDCPMC), hereby respectfully submits these comments in response to the notice entitled "Draft Guidances for Industry on Food-Contact Substance Notification System; Availability" published in the *Federal Register* on November 12, 1999 (64 Fed. Reg. 61648 (1999)). This notice requested comment concerning two draft guidance documents entitled "Preparation of Premarket Notifications for Food Contact Substances: Chemistry Recommendations" and "Preparation of Premarket Notifications for Food Contact Substances: Toxicology Recommendations," which were provided by the Food and Drug

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1/ The Society of the Plastics Industry, Inc. (SPI) is the trade association representing the fourth-largest manufacturing industry in the United States. SPI's 2,000 members represent the entire plastics industry supply chain, including processors, machinery and equipment manufacturers and raw material suppliers. The U.S. plastics industry employs 1.3 million workers and provides $274 billion in annual shipments. Founded in 1937, SPI is the voice of the plastics industry. The Food, Drug and Cosmetic Packaging Materials Committee is composed of representatives of SPI member companies with special interest and expertise in packaging materials for food and other FDA-regulated products.

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Administration (FDA) as part of its implementation of the Food-Contact Notification (FCN) process established by the FDA Modernization Act of 1997 (FDAMA) (Public Law 105-115).

It should be noted that, in addition to the members of the SPI Food, Drug and Cosmetic Packaging Materials Committee, these comments also reflect considerable input on the part of the chemists and toxicologists at Keller and Heckman, several of whom have had first-hand experience as reviewers and supervisors in FDA's branches dealing with food additive petitions. Thus, our recommendations are designed to take into account Agency policy including the sensible application of the principle of commensurate risk and regulation, *i.e.* the principle we understand to delimit data requests to what is needed to reach a sound conclusion on any toxicological or chemistry question, and to make it understood that, in evaluating data, FDA will exercise sound, well-rounded judgement on toxicological and related issues.[2/]

I. Guidance Document on Toxicology Recommendations

A. Format and Organization for Toxicology Data Package

FDA provides organizational and formatting guidelines for the toxicology data package in Section VI of the guidance. Specifically, the Agency recommends that the notifier submit a safety narrative, a comprehensive toxicology profile (CTP), and individual summaries of all unpublished study reports and published articles. Section IV Paragraph B elaborates on the content of the CTP, while Section VI Paragraph B describes the information that should be included in the individual summaries of study reports and published articles. There is substantial overlap in the requested information for the CTP and individual summary sections. Providing essentially the same detailed information in two portions of the toxicology data package will be unduly burdensome for the submitter and, further, will likely necessitate unnecessarily duplicative review on the part of Agency personnel. We are fearful that this could unduly prejudice timely reviews by the Agency.

As an alternative, it is recommended that the toxicology discussions in notifications consist of only two parts, a safety narrative stating in summary form the essential basis for the safety conclusion, and a section summarizing the specific studies that are relevant to the safety conclusion. Therefore, we respectfully urge that the Agency combine the two sections that are now designated as the "CTP" and "Individual summary of unpublished study reports and published articles" into one section in which relevant individual studies will be summarized. In this regard, we recommend that the concept of the CTP be retained, but with the modifications

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2/ *See* Alan M. Rulis, Ph.D., Acceptance Remarks for the 1999 International Achievement Award at the International Society of Regulatory Toxicology and Pharmacology, in which Dr. Rulis stated that "the principle of commensurate effort in the area of food ingredient safety is nowhere more critical than in the food packaging area."

described below, and that the requirement for additional individual study summaries be discarded as a redundancy.

B. Comprehensive Toxicology Profile

In Section IV Paragraph B of the guideline, which describes the information that should be included in the CTP, the Agency states that "CTPs should summarize and evaluate *all* toxicology studies and related information available on a particular substance. Studies or information . . . that identify adverse effects of the substance, or that bear significantly on the determination of an acceptable daily intake (ADI) for the substance, should be described in detail." Further, the guideline states that "[s]tudies and information that are determined to be of limited value should be described briefly." A literal reading of these recommendations would lead to the conclusion that **all** toxicity data on a particular substance must be provided in the CTP, even those studies that are not relevant to the safety determination. It is respectfully submitted that the submitter of a notification should not be required to discuss individual studies that are irrelevant to a sound analysis of the filing. It is reasonable for FDA to request the results of a literature search and a list of references to all other studies. To require a discussion of individual studies regardless of relevance, however, will impose a burdensome requirement of no decisional value so that neither the submitter nor the Agency should be required to supply or review such material. Indeed, FDA officials have stated that, where the dietary intake of chemicals is in the part per billion (ppb) range, such exposure is "of only marginal toxicological concern, unless the materials are known to be exquisitely toxic chemicals."[3/] We therefore respectfully request that the Agency explicitly state in the guidance that the submitter need only provide summaries of specific studies that are relevant to FDA's safety determination in the CTP.

For purposes of clarifying what information is relevant to FDA's safety determination, we recommend that the Agency's guidance specify the types of studies that should be addressed individually for each defined category of dietary concentration. In this regard, we request that the Agency amend the guidelines to align the required discussion of toxicology information in notifications with what has long been required for food additive petitions; doing so would be in conformance with the Agency's statement in the introduction to the toxicology guidelines to the effect that "[i]nformation in a PMN should be comparable to that required in a food additive petition."

More specifically, it is our view that, for those substances involving estimated dietary exposures (EDIs) below 0.5 ppb, only those studies bearing on a carcinogenicity determination or suggesting a toxicity concern at this low level of exposure can possibly be relevant. This is in accordance with FDA's Threshold of Regulation (TOR) policy where such a *de minimis* level of

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3/ *See* Alan M. Rulis, Ph.D., Acceptance Remarks for the 1999 International Achievement Award at the International Society of Regulatory Toxicology and Pharmacology.

exposure is considered substantial evidence that a substance is safe when used under its intended conditions of use, even in the absence of any toxicology data on the substance. Indeed, the Agency stated in the Preamble for the Threshold Rule its conclusion that the presence of a substance in the daily diet at or below 0.5 ppb is so negligible as to present no public health concerns. *See* 60 Fed. Reg. 36582 (1995).

For substances involving exposures between 0.5 ppb and 50 ppb in the diet, FDA traditionally has required the submission of acute data only; the Agency's guidance for FCN now recommends the submission of two in vitro genotoxicity tests. In this category, we recommend that the toxicology discussion should include summaries of the required individual genotoxicity studies and any other studies relevant to carcinogenicity. The notification also should address any studies that indicate other relevant toxicity concerns.

For exposures between 50 ppb and 1 part per million (ppm), FDA now recommends an in vivo genotoxicity study in addition to the two in vitro studies and two subchronic oral toxicity tests, one in a rodent species and one in a non-rodent species. It is reasonable for the CTP to include summaries of these studies, along with summaries of any other tests relevant to carcinogenicity and of tests that suggest potential concern about other types of toxicity that are relevant to FDA's safety determination.

While aligning the data requirements for notifications to that which has been traditionally required for food additive petitions would provide FDA with ample information to make a safety determination, a recently published paper by three officials at FDA's Center for Food Safety and Applied Nutrition provides the basis for increasing the upper bound level at which no toxicity data should be required and further allowing for flexibility in data requirements at all exposure levels. *See* M.A. Cheeseman *et al.*, A Tiered Approach to Threshold of Regulation, 37 Food and Chemical Toxicology 387 (1999). In this paper, the authors noted the highly conservative approach taken by FDA in setting the original threshold level and examined data on the 709 carcinogens listed in the Carcinogenic Potency Database (CPDB) compiled by Gold *et al.*[4/] They found that a particular set of criteria can be used to predict whether a substance that has not been the subject of full scale carcinogenicity testing is likely to be a carcinogen.

In particular, with respect to structure, it was found that most carcinogens can be grouped into one of seven classes of substances: N-nitroso compounds, strained heteronuclear rings, alpha-nitro-furans, polycyclic amines, hydrazines/triazenes/ azides/azoxy compounds, organophosphorous compounds and heavy metal-containing compounds. Thus, the structure of

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4/ *See* L.S. Gold and E. Zeiger (Eds), Handbook of Carcinogenic Potency and Genotoxicity Databases, CRC Press, Boca Raton, FL (1997).

an untested substance is a strong indicator of whether it is likely to be a carcinogen. Further, results of Ames assays and LD_{50}[5/] tests can indicate carcinogenic potency.

The authors concluded that the dietary threshold could be increased and developed a tiered threshold scheme based on the above predictive criteria. First, they recommended a dietary threshold of 4-5 ppb for those substances lacking structural alerts (*i.e.*, those substances not belonging to a structural class of substances known to be carcinogens) regardless of the results of an Ames assay, and those substances with structural alerts other than N-nitroso and benzidine-like compounds testing negative in the Ames assay. Second, for those substances testing negative in the Ames test and having an LD_{50} above 1000 mg/kg, they recommended a dietary threshold of 10-15 ppb.

The Cheeseman *et al.* study demonstrates that all factors identified as significant, *i.e.*, structure as well as available toxicity data, should be considered in their totality when making a safety determination. It follows that strict data requirements for each respective category of exposure levels can be regarded as unnecessary when all available information establishes that a substance is safe for its intended use. Therefore, we propose that the guidelines be revised to allow for flexibility in the dietary level at which no toxicity testing should be required in accordance with the factors identified in the paper by Cheeseman, *et al.* In addition, based on this study, we recommend that the guidance document provide for flexibility in the data requirements at all exposure levels, allowing the requirements to vary in appropriate cases based on the totality of information relevant to toxicity.

Finally, with respect to substances where FDA previously has reviewed safety data, it is our belief that it would be more appropriate to summarize the data on which FDA relied and discuss any relevant information that has become available since that time. Requiring an extensive summary in these situations would be unduly burdensome for all concerned.

C. Incremental Exposure ≤ 0.5 ppb

We recommend that FDA resolve what appears to be a conflict between the TOR policy and the new toxicology guidance regarding the evaluation of substances with exposures of less than 0.5 ppb. Specifically, based on the TOR policy, notifiers should not be required to calculate or utilize CEDIs for new uses with exposures below 0.5 ppb, nor should they be required to submit toxicity testing for substances involving such *de minimis* exposures.

In footnote 1 of the "Highlights" section, FDA acknowledges that cumulative "Threshold of Regulation" exposures (exposures of less than 0.5 ppb) from a limited number of trivial food additive uses are not likely to be more than negligible. Thus, under the TOR policy, FDA

5/ The LD_{50} is defined as the dose that induces death in 50% of dosed animals.

determined that it is not necessary to calculate the CEDI for exposures of less than 0.5 ppb. In footnote 1, FDA confirms that this determination remains sound. Nonetheless, the language used in the remainder of the guidance document, particularly in Section IV Paragraph C, purports to impose a requirement for the calculation of CEDIs in instances in which exposures for notified uses are less than 0.5 ppb. FDA states (in Footnote 1) that the CEDI approach taken under the FCN system does not conflict with the TOR approach, and there is no justification for distinguishing between the two systems with regard to exposure. The language should be clarified to leave no doubt but that the TOR approach will be continued.

Stated another way, it seems very clear that FDA clearly and correctly determined under the TOR that the conservatisms involved in estimating exposure make it unnecessary to add negligible exposure of 0.5 ppb or less. In our view, it is equally true under FCN as under TOR that cumulative negligible exposures are almost certain to remain negligible. Indeed, unless this policy is continued, it will be difficult or impossible to calculate accurate estimates of cumulative exposure at these very low levels, since the migration studies involved are likely to have non-detected findings in which actual migration is not quantitated. Adding "non-detected" exposures to other similar data results can only lead to gross overestimates that will serve no useful purpose. In short, in accordance with the position correctly taken by FDA under the TOR, in the absence of special unusual circumstances, CEDI calculations should not be required for notifications involving incremental exposure not exceeding 0.5 ppb. If FDA finds that specific substances are being notified in numbers that may generate more than a negligible CEDI, requiring additional toxicity data to support safety, such "wild Iris" instances should be handled on a case-by-case basis.

D. Genotoxicity Testing

The toxicologists who participated in the preparation of these comments continue to have conceptual reservations about the new genotoxic testing requirements for exposures above 0.5 ppb because of the ambiguities involved in analyzing the results of such tests and because of the possible low levels of correlation of the testing results to actual risks of cancer. Indeed, the FDA guideline offers little guidance as to how the recommended mutagenicity tests will be validated or interpreted. For instance, with respect to interpretation, if any one test is positive and others are negative, will the overall decision be based on a weight of evidence approach? Will a positive Ames test or positive micronucleus test be dispositive regardless of negative findings in other genotoxicity tests? The guidelines state (in Section IV Paragraph B) that, in determining whether results of genotoxicity tests indicate a potential carcinogenic concern for the substance, "the array of positive and negative genetic toxicity tests results" will be considered, among other factors. This wording suggests, but does not ensure, that a weight of the evidence, exercise of sound judgement approach will be used.

The findings of Cheeseman *et al.*, discussed above, demonstrate that various factors in addition to the results of a particular genotoxicity test may bear on the potential of a substance to be a carcinogen and its potency. Therefore, it follows that a weight of the evidence approach is most sensible in interpreting the results of genotoxicity screening tests. Such an approach will minimize the effect of a false positive on the validity of the entire test battery.

In the absence of a clear understanding by FDA as to how genotoxicity test results will be interpreted and applied, and the articulation of such an understanding in the guidance document, we urge that the Agency reconsider its mutagenicity testing requirements for food-contact substances. If these studies are to be required, FDA must explain how the various studies relate to each other and what additional data may be needed on the basis of "positive" results in one or more of the studies.

Finally, with respect to the genotoxicity testing recommendations, we request that the Agency amend the guidelines to state that, where the food-contact substance is a polymer, no genotoxicity testing will be required if (1) the monomer is not genotoxic and (2) there is effectively no migration of the oligomer at a suitably low level (*e.g.*, using a method with a limit of detection of 50 ppb in most cases) and, therefore, it is impractical to obtain sufficient amounts of low molecular weight material to perform studies. With regard to monomers, general agreement exists in the scientific community that polymers and even oligomers do not pose significant toxicology concerns if their monomers have been shown not to present such concerns. Further, with regard to oligomers, the most efficient way to obtain the material for toxicity testing is to extract it under the conditions of its intended use; however, if there is no detectable migration at a suitably low level, it becomes apparent that there will be *de minimis* exposure and that it will be impractical to acquire sufficient test material to perform meaningful tests.

E. Risk Assessment for Carcinogenic Constituents

In Section IV Paragraph D of the guideline, in which the Agency describes those circumstances where a risk assessment will be required for the carcinogenic constituents of food-contact substances, FDA states that "[i]f the calculated upper bound, lifetime risk of a constituent is less than 10^{-8}, the risk associated with the constituent will generally be considered insignificant." Long-standing, time-tested and court-approved FDA policy has established 10^{-6} as the standard for such a determination,[6/] and no rationale has been given for making a change in a standard that

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[6/] *See* 50 Fed. Reg. 51511 (1985), in which the Agency takes the position that the 10^{-6} upper bound risk for methylene chloride consumed in decaffeinated coffee is *de minimis* and, therefore, consistent with the principle of a reasonable certainty of no harm. In this notice, the Agency further cites the use of the 10^{-6} upper bound risk in formulating the diethylstilbestrol (DES) proviso of the Delaney Clause and its use in the assessment for the rulemaking on D&C Green

(continued...)

has acquired important secondary meaning. Although it is unclear whether this statement represents an intentional change in policy or not, the reference in the guidance to a 10^{-8} standard could lead the reader to conclude that the Agency is indeed propounding a change of policy in this area and could make it appear that its long time reliance and citation in many regulatory preambles of this standard has suddenly, and without reason, been declared erroneous. Since a guidance document clearly is not the appropriate place to make such a change in an arbitrary way, it is respectfully requested that the sentence in question be eliminated from the guidance entirely.

F. Effect of Equivocal Carcinogenicity Data on Food-Contact Substances

The Agency describes in Section VII of the toxicology guideline those instances where the premarket review and approval of a food additive petition, rather than a notification, may be necessary for the Agency to make an adequate determination on the safety of a food-contact substance. One instance given is where "there are one or more carcinogenicity studies on the [food-contact substance] that have not been previously reviewed by the Agency and which are not clearly negative for carcinogenicity." We recommend including in this portion of the guidance an explanation that a petition may be required only when the equivocal data concerns a substance that is not merely a "constituent" as that term has long been defined under the Agency's well-established "Constituents Policy," "constituent" meaning a substance that is a non-functional and unwanted component of a food-contact article, such as a low level of unreacted monomer. *See* 47 Fed. Reg. 14,464 (1982).

II. Guidance Document on Chemistry Recommendations

The following comments relate to the draft Chemistry Guidance document, specifically with regard to Table I in Appendix IV, which sets forth consumption factors (CF). First, concerning the subdivision of the CF for polyvinyl chloride (PVC), it is our view that the two subcategories should be identified as "rigid and semirigid" and "plasticized" rather than "rigid" and "semirigid." The two suggested subcategories more appropriately reflect the uses and migration characteristics of PVC. Furthermore, the current description would not easily permit the proper evaluation of plasticized PVC, which is sometimes referred to as flexible PVC, as it is usually not referred to as "semirigid."

In addition, the subdivision of the polystyrene CF, which currently includes the subcategories "impact" and "non-impact," should be extended. Specifically, the "non-impact" subcategory should itself be subdivided into "general purpose polystyrene" (GPPS) and polystyrene "foam." We believe that the same data that FDA relied upon in creating the "impact" and "non-impact" categories, with CF values of 0.04 and 0.06, respectively, contained in

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[6/](...continued)
No. 6.

information provided by the Styrene Migration Task Group of SPI's Food, Drug, and Cosmetic Packaging Materials Committee, allows the further division of the 0.06 "non-impact" CF into CF values of 0.02 for GPPS and 0.04 for polystyrene foam.

It is also submitted that the CF for polypropylene (PP) in the draft document, 0.04, should be changed to 0.02, the PP CF appearing in prior versions of the guidance documents regarding chemistry information. We believe that the 0.04 value contained in the guidance document is derived from a report provided to FDA regarding food-contact application of polyolefins. Although the report submitted by SPI derived a total CF of 0.04 for PP, it also demonstrated that 62.5% of that value (*i.e.*, 0.025) is for dry food and that 37.5% of that value (*i.e.*, 0.015) is applied to aqueous and fatty foods (the foods for which migration testing is required and exposure is calculated).[7/] Therefore, we recommend that the CF be returned to the 0.02 value that FDA currently and properly has been applying to PP.

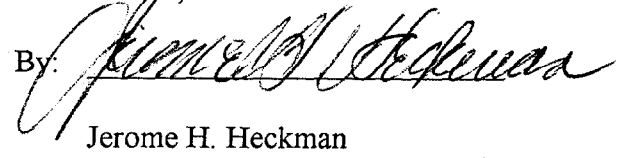
Finally, we submit that the data provided by SPI to FDA amply demonstrates that the CF for the "Microwave susceptor" category should be 0.001 instead of the 0.01 value in the draft document. (*See* attached March 23, 1994 letter to Dr. Edward Machuga).

* * *

SPI appreciates the opportunity to comment on FDA's draft chemistry and toxicology guidelines for the preparation of Food-Contact Notifications for food-contact substances. The Society would be pleased to respond to requests from the Agency for additional information relating to these comments.

Respectfully submitted,

THE SOCIETY OF THE PLASTICS INDUSTRY, INC.

By: 

Jerome H. Heckman
GENERAL COUNSEL

7/ FDA generally does not recommend migration testing for contact with dry food having no free surface fat or oil.

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Mar 23 1 01 PM '94

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Center for Food Safety and
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The Food and Drug Administration
1110 Vermont Avenue, N.W., 12th Floor
Washington, D.C. 20036

Re: Susceptor Microwave Packaging; FAMF No. 373

Dear Dr. Machuga:

The purpose of this letter is to follow up on our recent telephone conferences regarding the Food and Drug Administration's (FDA) need for updated information on the use of microwave susceptor packaging, and on your request for our assistance in collecting such data. In this regard, we understand that the Agency is primarily interested in susceptor packaging used for foods other than popcorn since the popcorn packages are not likely to result in much, if any, exposure to polyethylene terephthalate (PET) oligomers. (Our assumption here is that potential migration of these oligomers is what has prompted most of your colleagues' concerns.) As discussed more fully below, we have collected information on both popcorn and non-popcorn products sold in susceptor packaging. Using these data, we have calculated that the maximum percentage of the daily diet in contact with susceptor packaging is conservatively placed at 0.1%.

Non-Popcorn Susceptors

For non-popcorn susceptors, we surveyed knowledgeable individuals about the current use of susceptor packaging. Due to the limited number of susceptor packaging manufacturers, we obtained an accurate estimate of the total volume of food, other than popcorn, packaged with susceptors. This volume is placed at

94,156 tons. We understand that this estimate was derived by multiplying the number of packages produced in 1993 by the weight of the packaged food. This figure in turn allowed us to calculate a consumption factor (CF) of 0.031% as follows:

(94,156 tons of food/year x 2000 lbs/ton x 453 g/lb x 100%) ÷ (250 x 10^6 people x 365 days/year x 3000 g food/person/day) = 0.031%

Please note that these calculations overestimate the quantity of food packaged in susceptors because when several weights of food are packaged in a given package, the highest weight was chosen for the calculations. Further, we have been advised by industry sources that the market for these containers is declining, not increasing.

Popcorn Susceptors

With regard to the volume of microwave popcorn consumed per year, we have been advised by the Popcorn Institute that the popcorn crop for the three year period 1990, 1991, and 1992, was 918 million pounds, 668 million, and 1,115 million pounds, respectively, with an average of 900 million pounds per year for the three year period. Of this amount, 25% was exported and the remaining 75% was sold domestically. Forty percent of the domestic popcorn was sold into commercial markets (movie theaters, concessionaires, etc.), and the remaining 60% was marketed to consumers for home consumption. To be conservative, we assumed that all consumer popcorn is sold in susceptor packaging.

With this information we have calculated a CF of 0.067% for the popcorn susceptor market as follows:

(900 x 10^6 lbs popcorn/year x 453 g/lb x 0.75 (domestic) x 0.60 (microwaved) x 100%) ÷ (250 x 10^6 people x 365 days/year x 3000 g/day/person) = 0.067%.

We also were provided data that allowed us to calculate a CF using a different approach. Specifically, we have been advised that the number of microwave popcorn bags distributed per year is approximately 1.6 billion. Using an average of 3.4 ounces of popcorn per bag, we have calculated a CF for microwave popcorn of 0.056% as follows:

(1.6 x 10^9 bags/year x 3.4 ounces/bag x 28.35 g/ounce x 100%) ÷ (250 x 10^6 people x 365 days/year x 3000 g/day/person) = 0.056%

This factor, although somewhat less than the CF of 0.067% calculated above, is probably more accurate because the previous calculation assumed conservatively that all retail popcorn is cooked in susceptors.

Overall CF for Microwave Susceptors

Combining the non-popcorn susceptor CF of 0.031% and the more conservative popcorn susceptor CF of 0.067% yields an overall CF of 0.098%. Therefore, it seems quite clear that a CF of 0.1% is a conservative estimate of the percentage of the daily diet packaged in microwave susceptors.

* * *

We hope the Agency finds these data helpful in reaching a conclusion concerning the safety of susceptor packaging but we do stand ready to provide further assistance, if needed. When you reach a point where you have received enough information to make some tentative conclusions, several members of our committee have indicated that they would like to meet with you so there can be a full exchange of views on this subject. Here again, if you will let us know whenever you think that such a meeting would be in order, we will be glad to make the necessary arrangements.

Sincerely yours,

Jerome H. Heckman